(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 February 2006 (16.02.2006)

PCT

(10) International Publication Number
WO 2006/017257 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2005/024624

(22) International Filing Date: 11 July 2005 (11.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/587,329 12 July 2004 (12.07.2004) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/017257 A2

(54) Title: AZETIDINONE DERIVATIVES

(57) Abstract: Novel azetidinone-containing compounds are useful in the treatment or prevention of various human diseases. For example, they can be employed in lowering plasma levels of a sterol, such as cholesterol. Thus, these compounds can be administered in the contexts of methods for treating and/or preventing diabetes, obesity, and atherosclerosis, respectively.

AZETIDINONE DERIVATIVES

FIELD OF THE INVENTION

[0001] The present invention relates to novel pharmaceutical compounds useful in the treatment of human diseases.

BACKGROUND OF THE INVENTION

[0002] The information provided herein and references cited are provided solely to assist the understanding of the reader, and does not constitute an admission that any of the references or information is prior art to the present invention.

[0003] Atherosclerotic coronary heart disease represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigarette smoke, and serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk.

[0004] Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a key step in the intestinal absorption of dietary cholesterol.

[0005] Certain azetidinone-containing compounds have been reported as being useful in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. Synthetic methods, including stereospecific routes, for preparing certain azetidinone compounds have also been reported. The following are exemplary disclosures that discuss various azetidinone derivatives and various synthetic routes for preparing such compounds.

[0006] U.S. Patent No. 4,983,597 discloses N-sulfonyl-2-azetidinone containing compounds as anti-cholesterolemic agents.

[0007] Castañer et al. (Drugs of the Future, 25(7): 679-685, (2000)) discloses diphenylazetidinone derivatives, such as ezetimibe, for treating hyperlipidemia, arteriosclerosis, and hypercholesterolemia.

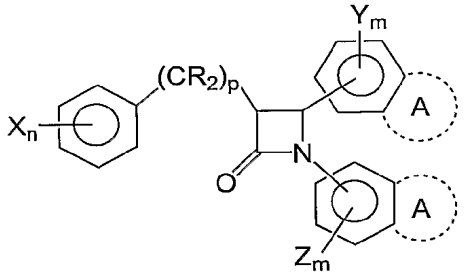
[0008] U.S. Patent No. 5,728,827 discloses a process for producing certain azetidinone-containing compounds under neutral conditions.

[0009] U.S. Patent No. 5,561,227 discloses a stereospecific process for producing certain azetidinone-containing compounds.

SUMMARY OF THE INVENTION

[0010] The present invention provides novel azetidinone containing compounds and methods for the preparation and use thereof. Compounds presented herein may be useful in the treatment of various diseases. In certain embodiments, invention compounds are employed as hypocholesterolemic agents, and as such, can be utilized to reduce levels of sterols, such as cholesterol, in the plasma of a mammal. Accordingly, compounds presented herein may be administered to treat and/or prevent indications such as hyperlipidemia (*e.g.*, atherosclerosis, hypercholesterolemia, or sitosterolemia), inflammation, stroke, diabetes, obesity, and the like.

[0011] An aspect of the invention is drawn to compounds corresponding to Formula (I):



(I)

and stereoisomers, tautomers, solvates, prodrugs, pharmaceutically acceptable salts and mixtures thereof; wherein:

A at each occurrence independently forms an optionally substituted fused heterocycle with the phenyl to which it is attached, wherein the dashed lines represent an optionally present A, provided, however, that at least one A is present;

R at each occurrence is selected from the group consisting of H, halogen, OH, NH_2, NO_2, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

X, Y, and Z at each occurrence are independently selected from the group consisting of halogen, OH, alkyl, alkoxy, SH, thioalkyl, NH_2, and NO_2;

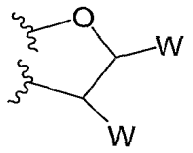
m at each occurrence is independently 0 to 3;

n is 0 to 5; and

p is 1 to 6.

[0012] In some embodiments of compounds of Formula (**I**) at least one X is halogen, such as when X is F and n is 1. Other embodiments of compounds of Formula (**I**) include compounds where at least one Y is OH. In still other embodiments, compounds of Formula (**I**) also include compounds where at least one Z is halogen, such as F. Additionally compounds of Formula (**I**) include compounds where at least one R is OH, such as where $(CR_2)_p$ is $-CH_2-CH_2-CH(OH)-$.

[0013] In some embodiments of compounds of Formula (**I**), A forms a nonaromatic optionally substituted fused heterocycle such as an optionally substituted fused five-membered heterocycle. For example, in some such embodiments A is:



wherein:

W at each occurrence is independently selected from the group consisting of H, halogen, OH, alkyl, alkoxy, SH, thioalkyl, NH_2, NO_2, CN, SO_2R^1, SO_3R^2, and $-J-C(O)R^3$;

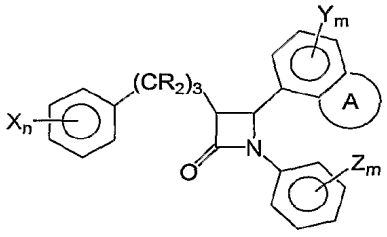
R^1 is selected from the group consisting of H, halogen, alkyl, alkoxy, aryl, heteroaryl, NH_2, NH(alkyl), and $N(alkyl)_2$;

R^2 is selected from the group consisting of H, NH_2, NH(alkyl), and $N(alkyl)_2$;

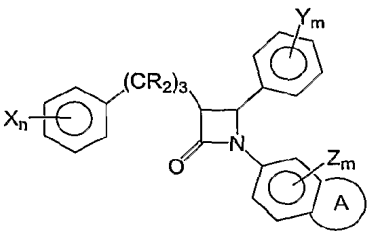
J is selected from the group consisting of a covalent bond and C_1-C_3 alkylene; and

R^3 is selected from the group consisting of OH, alkoxy, NH_2, NH(alkyl), and $N(alkyl)_2$.

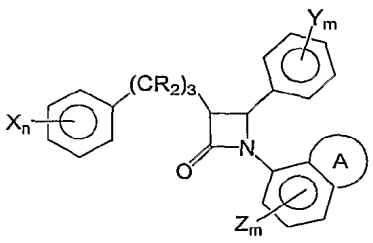
[0014] Additional embodiments of Formula (**I**) include compounds corresponding to Formulas (**II**), (**III**), or (**IV**) which comprise the structures shown below:



(**II**)

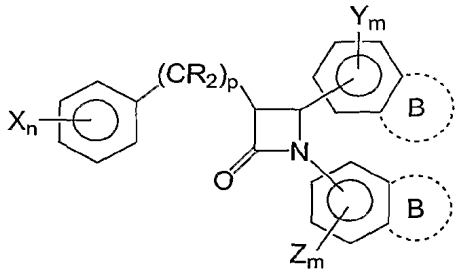


(**III**)



(**IV**).

[0015] Yet another aspect of the invention is drawn to compounds corresponding to Formula (**V**):



(**V**)

wherein:

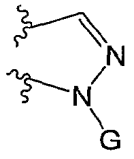
B at each occurrence is independently a G-substituted five-membered fused heterocycle, wherein the dashed lines represent an optionally present B, provided, however, that at least one B is present;

G is selected from the group consisting of -(C_1-C_3 alkylene)-C(O)R^4 and -(C_1-C_3 alkylene)-SO_2R^4; and

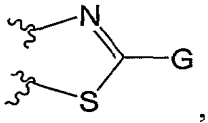
R^4 is selected from the group consisting of H, hydroxyl, halogen, alkyl, alkoxy, aryl, heteroaryl, NH_2, NH(alkyl), and N(alkyl)$_2$.

[0016] In some embodiments, compounds of Formula (**V**) include compounds where at least one X is halogen, such as when X is F and n is 1. Further embodiments of Formula (**V**) include compounds where at least one R is OH, such as where $(CR_2)_p$ is -CH_2-CH_2-CH(OH)-. Still other embodiments of Formula (**V**) include compounds where Y is OH and m is 1.

[0017] Typical embodiments include compounds where B is a G-substituted pyrazole or thiazole, such as when B is:



or



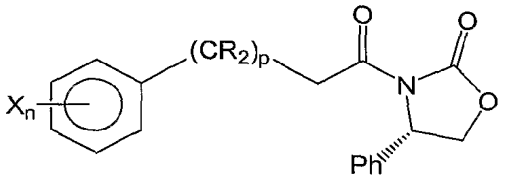
,

wherein G is –CH_2-C(O)R^4 or -CH_2-SO_2R^4.

[0018] Embodiments include compositions comprising invention compounds and a pharmaceutically acceptable carrier; pharmaceutical compositions comprising invention compounds and a pharmaceutically acceptable carrier; and kits comprising a vessel containing invention compounds.

[0019] An aspect of the invention is drawn to methods of treating and/or preventing diabetes, obesity, or lowering concentration of a sterol, such as cholesterol, in plasma of a mammal, by administering a therapeutically effective amount of a compound presented herein. Some embodiments include methods of treating and/or preventing atherosclerosis by administering a therapeutically effective amount of a compound presented herein.

[0020] The present invention also provides methods for preparing a compound presented herein by contacting a compound of Formula (**VI**) with an imine of Formula (**VII**) or (**VIII**), in the presence of a Lewis acid, a silylating agent, and a fluoride ion catalyst,
wherein said compound of Formula (**VI**) corresponds to the following structure:



(**VI**)

wherein:

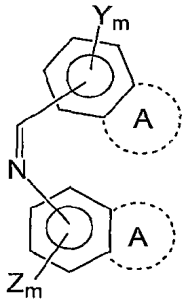
R at each occurrence is independently selected from the group consisting of H, halogen, OH, NH_2, NO_2, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

X is optionally present, and when present at each occurrence is independently selected from the group consisting of halogen, OH, alkyl, alkoxy, SH, thioalkyl, NH_2, and NO_2;

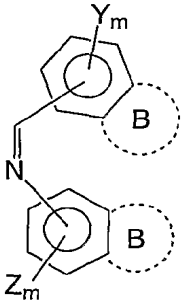
n is 0 to 5; and

p is 1 to 6;

wherein said imine of Formula (**VII**) or (**VIII**) corresponds to the following structures:



(**VII**)



(**VIII**)

wherein:

A at each occurrence independently forms an optionally substituted fused heterocycle with the phenyl to which it is attached, wherein the dashed lines represent an optionally present A, provided, however, that at least one A is present;

B at each occurrence is independently a G-substituted five-membered fused heterocycle, wherein the dashed lines represent an optionally present B, provided, however, that at least one B is present;

G is selected from the group consisting of $-(C_1\text{-}C_3$ alkylene)-$C(O)R^4$ and $-(C_1\text{-}C_3$ alkylene)-SO_2R^4;

R^4 is selected from the group consisting of H, hydroxyl, halogen, alkyl, alkoxy, aryl, heteroaryl, NH_2, NH(alkyl), and $N(alkyl)_2$,

Y and Z are optionally present, and when present at each occurrence are independently selected from the group consisting of halogen, OH, alkyl, alkoxy, SH, thioalkyl, NH_2, and NO_2; and

m at each occurrence is independently 0 to 3.

[0021] In some embodiments, methods for preparing invention compounds include methods wherein the Lewis acid is titanium (IV) chloride, the silylating agent is trimethylsilyl chloride (TMSCl), and the fluoride ion catalyst is tetrabutyl ammonium fluoride (TBAF). Methods for preparing invention compounds may be performed in a single-step or multi-step fashion. For example, preparative methods provided herein can be conducted in two steps.

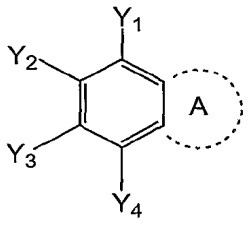
DETAILED DESCRIPTION OF THE INVENTION

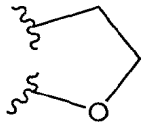
I. INVENTION COMPOUNDS

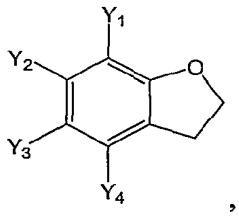
[0022] In this description, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For instance, if a group is defined to include hydrogen or H, it also can include deuterium and tritium.

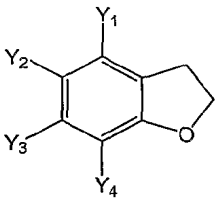
[0023] Compounds of the present invention may have asymmetric centers and may occur, except when specifically noted, as mixtures of stereoisomers or as individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention. Compounds of the present invention embrace all conformational isomers. Compounds of the present invention may also exist in one or more tautomeric forms, including both single tautomers and mixtures of tautomers.

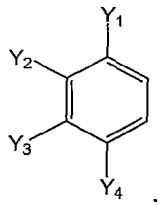
[0024] As employed herein, points of attachment to phenyl rings in invention compounds are denoted by "~~~~". Accordingly, any carbon or heteroatom adjacent to a "~~~~" indicates a carbon or heteroatom, respectively, attached to the phenyl ring in an invention compound. As an example, the following formula:



where A is 

embraces 

, 

, and 

.

Additionally, as employed herein, points of attachment are also denoted by "-". Accordingly, any carbon or heteroatom adjacent to a "-" indicates a carbon or heteroatom, attached respectively. As an example, the formula $(CR_2)_p$, where p is 3 and at least one R is OH, embraces $-CH_2-CH_2-CH(OH)-$, $-CH_2-CH(OH)-CH_2-$, and $-CH(OH)-CH_2-CH_2-$.

[0025] The term "heterocycle" or "heterocyclic" refers to cyclic hydrocarbyl compounds of which at least one ring member is a heteroatom. Heterocyclic groups include monocyclic, bicyclic, and polycyclic ring compounds containing from 3 to 20 ring members of which one or more ring member is a heteroatom such as, but not limited to, N, O, and S. Heterocyclic groups include any level of saturation, including non-aromatic (i.e., saturated or partially saturated) and aromatic. Accordingly, heterocycle embraces heteroaryl, defined below. For instance, heterocyclic groups include unsaturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms; saturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms; condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms; unsaturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms; saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms; unsaturated 3 to

8 membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms. Preferred heterocycles contain 5 ring members. Examples of heterocyclic groups include, but are not limited to, 2,4-dihydrofuran. Heterocycles embrace substituted heterocycles or substituted heterocyclic groups according to the definition of "substituted" provided below.

[0026] The term "substituted" refers to an atom or group of atoms that has been replaced with another substituent. "Substituted" comprehends any level of substitution, *e.g.*, mono-, di-, tri-, tetra-, or penta-substitution, where such substitution is chemically permissible. Substitutions can occur at any chemically accessible position and on any atom, such as substitution(s) on carbons or any heteroatom. For example, substituted compounds are those where one or more bonds to a hydrogen or carbon atom(s) contained therein are replaced by a bond to non-hydrogen and/or non-carbon atom(s). Substitutions can include, but are not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups.

[0027] The term "hydrocarbyl" refers to any organic radical having a directly attachable carbon atom to any molecule presented herein. The phrase "substituted hydrocarbyl" refers to a hydrocarbyl group that is substituted according to the definition provided above. Hydrocarbyl groups include saturated and unsaturated hydrocarbons, straight and branched chain aliphatic hydrocarbons, cyclic hydrocarbons, and aromatic hydrocarbons.

[0028] The term "alkyl" refers to hydrocarbyl chains comprising from 1 to 20 carbon atoms. "Alkyl" includes straight chain alkyl groups, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, and the like. The term also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, and $-CH_2CH(CH_3)_2$. Thus, alkyl groups include primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Preferred alkyl groups include alkyl groups having from 1 to 3 carbon atoms, such as methyl, ethyl, and propyl.

Alkyl groups embrace "substituted alkyl" group, wherein an alkyl group is substituted according to the definition provided above.

[0029] The term "alkylene" refers to a divalent alkyl group, as defined above.

[0030] The term "alkoxy" refers to an oxygen-containing alkyl group, as defined above, with structure –O-alkyl.

[0031] The term "thioalkyl" refers to a sulfur-containing alkyl group, as defined above, with structure –S-alkyl.

[0032] The term "halogen" refers to a substituent selected from F, Cl, I, or Br. A preferred halogen is F.

[0033] The term "aryl" refers to aromatic radicals that comprise from 3 to 20 carbon atoms. Aryl groups include monocyclic, bicyclic, or polycyclic aromatic rings, such as, but not limited to, phenyl, biphenyl, anthracenyl, and naphthenyl. Aryl groups embrace "substituted aryl group", which refers to an aryl group that is substituted according to the definition provided above. For example, substituted aryl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) and also includes aryl groups in which one or more aromatic carbons of the aryl group is bonded to a substituted and/or unsubstituted alkyl, alkenyl, or alkynyl group.

[0034] The term "heteroaryl" refers to (i) a 3 to 20-membered aromatic ring comprising carbon atoms and heteroatoms, such as N, S, and O or (ii) an 8- to 10-membered bicyclic or polycyclic ring system containing carbon atoms and heteroatoms, such as N, S, and O, wherein at least one of the rings in the bicyclic system is an aromatic ring. The heteroaryl ring may be attached at any heteroatom or carbon atom. Representative heteroaryl compounds include, for example, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, thiophenyl, thiazolyl, furanyl, pyridofuranyl, pyrimidofuranyl, pyridothienyl, pyridazothienyl, pyridooxazolyl, pyridazooxazolyl, pyrimidooxazolyl, pyridothiazolyl, pyridazothiazolyl, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, and 2H-1,2,3-triazolyl), tetrazolyl, (e.g. 1H-tetrazolyl and 2H tetrazolyl), pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, and 1,2,5-oxadiazolyl), benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g. 2H-1,4-benzoxazinyl),

thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, and 1,2,5-thiadiazolyl). Heteroaryl groups embrace "substituted heteroaryl", which refers to a heteroaryl group that is substituted according to the definition provided above. The term heterocycle embraces heteroaryl, and the term substituted heterocycle embraces substituted heteroaryl.

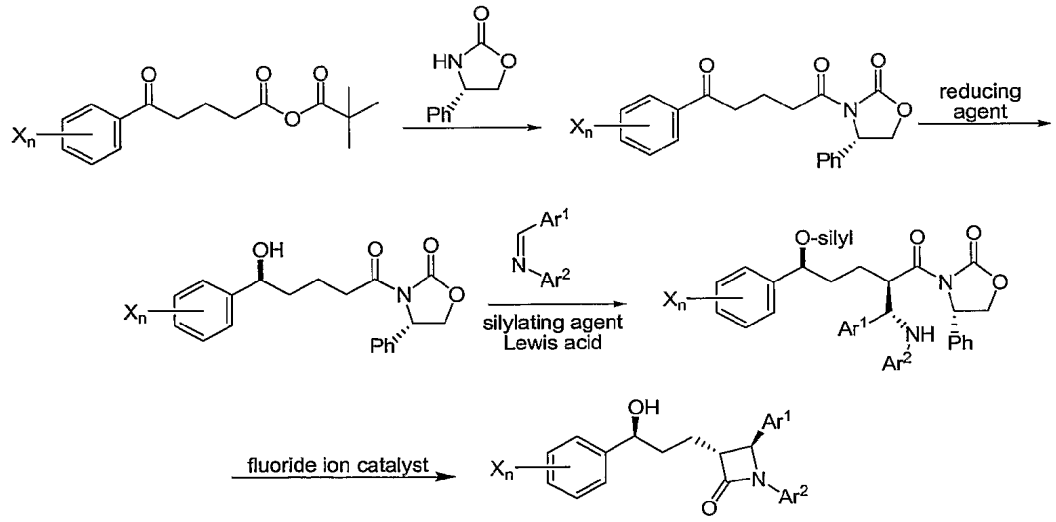
II. PREPARATION OF INVENTION COMPOUNDS

[0035] Presented below are exemplary general schemes for the preparation of invention compounds. Further details of synthetic methods are provided in the Examples, below. Since invention compounds can be readily prepared according to procedures well known to those skilled in the art, numerous methods, in lieu of or in addition to the synthetic schemes presented below, may be employed to prepare the compounds in question.

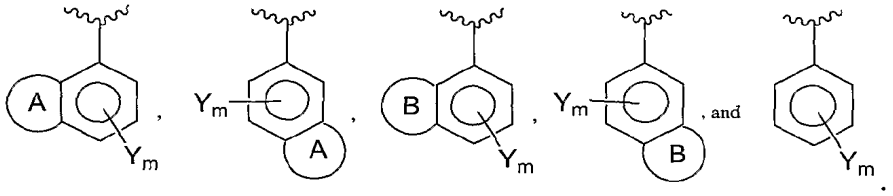
[0036] Derivatives and chemically similar compounds within the scope of the instant disclosure may be prepared by routine modification of the procedures provided herein using the appropriate starting materials, the selection of which will be evident to those of skill in the art.

[0037] Invention compounds may be prepared according to the representative stereospecific route depicted below in Scheme 1.

SCHEME 1



wherein $Ar^{\cdot}$ and Ar^{-} are each independently selected from the following:



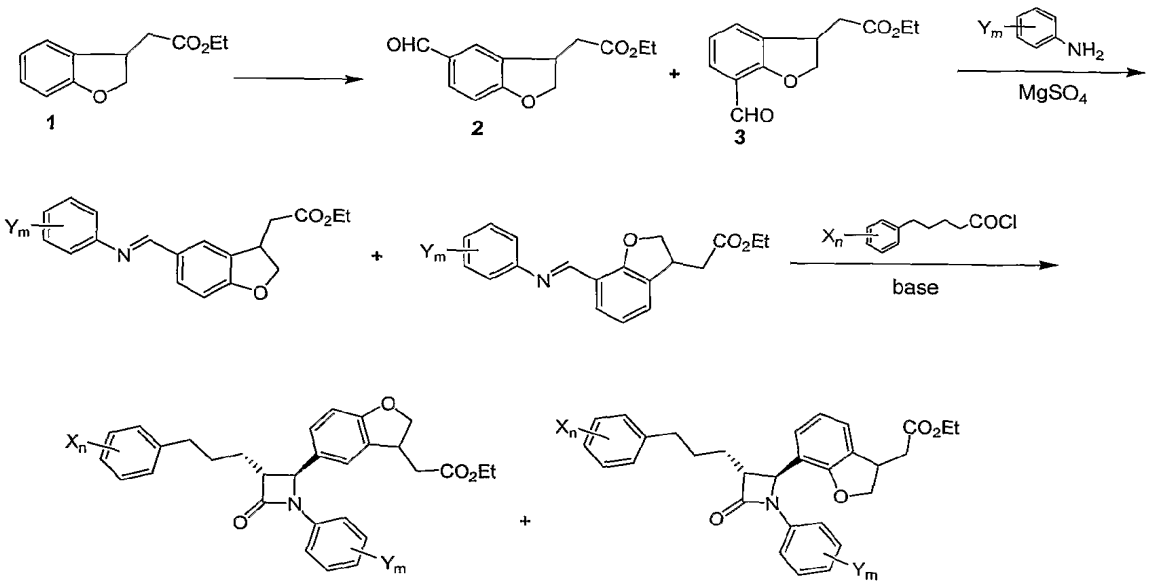
[0038] The phrase "Lewis acid" refers to any species with a vacant orbital. Exemplary Lewis acids include CO_2, $SnCl_2$, SO_3, BF_3, $AlCl_3$, PF_5, and the like. A preferred Lewis acid for use in preparative methods described herein include titanium (IV) chloride.

[0039] The phrase "silylating agent" refers to any hydrocarbyl compound containing silicon. Exemplary silylating agents include 3-aminopropyltriethoxysilane, 1,3-bis(chloromethyl)tetramethyl-disilazane, bis(diethylamino)dimethylsilane, N,O-bis(trimethylsilyl)acetamide, bis(trimethylsilyl)sulfate, and the like. A preferred silylating agent for use in preparative methods described herein include trimethylsilyl chlorides (TMSCl).

[0040] The phrase "fluoride ion catalyst" refers to any catalyst which provides a fluoride ion. Exemplary fluoride ion catalysts include phenyl fluorine, norbornyl fluorine, tetrabutyl ammonium fluoride (TBAF), and the like. In some embodiments, the fluoride ion catalyst for use in preparative methods described herein is tetrabutyl ammonium fluoride (TBAF).

[0041] In addition to the route depicted in Scheme 1, invention compounds may alternatively be prepared according to the representative route depicted below in Scheme 2.

SCHEME 2



III. THERAPEUTIC APPLICATIONS

[0042] Compounds and compositions of the instant invention may be used to treat and/or prevent a variety of disorders. The term "treating" refers to ameliorating, reducing, or halting the progression of one or more symptoms associated with the disorder to be treated. Compounds and compositions that may be used in therapeutic applications have reasonably high bioavailability in a target tissue and acceptably low toxicity. Those skilled in the art can assess compounds described herein for their pharmaceutical acceptability using standard methods.

[0043] Typically, compounds of the instant invention are used in the treatment of hyperlipidemia, such as atherosclerosis, hypercholesterolemia, or sitosterolemia, inflammation, stroke, diabetes, obesity, and the like. Compounds of the invention can be utilized to reduce levels of sterols, such as cholesterol, in the plasma. Those skilled in the art can determine other diseases and disorders for which administration of compounds or compositions described herein can be beneficial.

[0044] The term "therapeutically effective amount" refers to an amount of an invention compound described herein sufficient to exert a therapeutically useful effect on the patient treated. The therapeutically effective concentration may be determined empirically by testing

the compounds in *in vitro* and *in vivo* systems described herein and then extrapolated therefrom for dosages for humans.

[0045] The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

[0046] For instance, a therapeutically effective amount should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50- 100 μg/ml. Pharmaceutical compositions should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 0.01 mg, 0.1 mg or 1 mg to about 500 mg, 1000 mg or 2000 mg, and in one embodiment from about 10 mg to about 500 mg of the active ingredient or a combination of essential ingredients per dosage unit form.

IV. PHARMACEUTICAL COMPOSITIONS

[0047] The phrase "pharmaceutically acceptable carrier" refers to any carrier known to those skilled in the art to be suitable for the particular mode of administration. Invention compounds may optionally be formulated with at least one pharmaceutically acceptable carrier in compositions provided herein.

[0048] Compounds described herein may be prepared and/or administered as a pharmaceutically acceptable salt. The phrase "pharmaceutically acceptable salt" refers to any salt preparation that is appropriate for use in a pharmaceutical application. Pharmaceutically-acceptable salts include amine salts, such as N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-*p*-chloro-benzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine, tris(hydroxymethyl)aminomethane, and the like; alkali metal salts, such as lithium, potassium, sodium, and the like; alkali earth metal salts, such as barium, calcium, magnesium, and the like; transition metal salts, such as zinc, aluminum, and the like; other metal salts, such as sodium hydrogen phosphate, disodium phosphate, and the like; mineral acids, such as hydrochlorides, sulfates, and the like; and salts of organic acids, such as acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, fumarates, and the like.

[0049] Compositions herein comprise one or more compounds provided herein. The compounds can be formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Invention compounds may be formulated into pharmaceutical compositions using techniques and procedures well known in the art. For example, see Ansel, INTRODUCTION TO PHARMACEUTICAL DOSAGE FORMS, 4th Ed. (1985), at 126.

[0050] In compositions, one or more invention compounds is (are) mixed with a suitable pharmaceutical carrier. The compounds may be derivatized as the corresponding salts, esters, enol ethers or esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, or hydrates prior to formulation. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of diseases or disorders to be treated.

[0051] Compositions can be formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected carrier at an effective concentration, such that the treated condition is relieved or prevented, or that one or more symptoms are ameliorated.

[0052] The invention also encompasses prodrugs of a compound of the invention which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of a compound of the invention which are readily convertible *in vivo* into a compound of the invention. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in DESIGN OF PRODRUGS, H. Bundgaard (ed.), Elsevier, 1985.

V. THERAPEUTIC ADMINISTRATION

[0053] Invention compounds may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage

and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. Concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are illustrative only and are not intended to limit the scope or practice of the claimed compositions.

[0054] In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate.

[0055] Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion, or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[0056] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are, in one embodiment, formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms

include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

[0057] Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrin derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents.

[0058] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition, 1990.

[0059] Dosage forms or compositions containing active compounds in the range of 0.005% to 100% (wt%) with the balance made up from non-toxic carrier may be prepared. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% (wt%) active compound, in one embodiment 0.1-95% (wt%), in another embodiment 75-85% (wt%).

VI. COMBINATION THERAPY

[0060] In another embodiment, invention compounds may be administered in combination, or sequentially, with another therapeutic agent. For example, the composition or treatment can further comprise one or more cholesterol biosynthesis inhibitors co-administered, simultaneously or sequentially, with invention compounds.

[0061] Non-limiting examples of cholesterol biosynthesis inhibitors for use in the compositions and methods of the present invention include competitive inhibitors of HMG CoA reductase (the rate-limiting step in cholesterol biosynthesis), squalene synthase inhibitors, squalene epoxidase inhibitors, and mixtures thereof. Non-limiting examples of suitable HMG CoA reductase inhibitors include statins such as lovastatin (for example MEVACOR™ which is available from Merck & Co.), pravastatin (for example PRAVACHOL™ which is available from Bristol Meyers Squibb), fluvastatin, simvastatin (for example ZOCOR™ which is

available from Merck & Co.), atorvastatin, cerivastatin, CI-981, ZD4522, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyri- din-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin, pitavastatin (such as NK-104 of Negma Kowa of Japan); HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxymethyl)-4'-oxo-2'R-oxetanyl]-3,5- ,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-- 5-yl)methoxy]benzene-methanamine hydrochloride) and other sterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors include lovastatin, pravastatin, fluvastatin, atorvastatin, and simvastatin.

[0062] Total daily dosage of cholesterol biosynthesis inhibitor(s) can range, for example, from about 0.1 to about 160 mg per day, and preferably about 0.2 to about 80 mg/day in single or 2-3 divided doses. In an embodiment, cholesterol biosynthesis inhibitors can be administered at a lower total daily dosage when co-administered with invention compounds.

[0063] In another embodiment, the compositions or methods of the present invention can further comprise one or more peroxisome proliferator-activated receptor (PPAR) activators (such as fibrates), bile acid sequestrants (such as cholestyramine), ileal bile acid transport (IBAT) inhibitors (such as benzothiepines) or apical sodium co-dependent bile acid transport (ASBT) inhibitors, nicotinic acid (niacin) and/or derivatives (such as niceritrol, nicofuranose and acipimox), acylCoA:cholesterol O-acyltransferase (ACAT) inhibitors (such as avasimibe), cholesteryl ester transfer protein (CETP) inhibitors, probucol or derivatives, low-density lipoprotein (LDL) receptor activators, fish oil or omega 3 fatty acids, natural water soluble fibers, such as psyllium, guar, oat and pectin, plant sterols, plant stanols and/or fatty acid esters of plant stanols, antioxidants, monocyte and macrophage inhibitors, hormone replacement agents such as androgens, estrogens, progestins, their pharmaceutically acceptable salts and derivatives, obesity control medications such as noradrenergic agents, serotonergic agents and thermogenic agents, blood modifiers (such as anti-coagulants, antithrombotics and aspirin), cardiovascular agents (such as calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors), anti-diabetic medications (such as sulfonylureas, e.g. glimepiride or glipizide, and insulin) co-administered simultaneously or sequentially with invention compounds.

[0064] Mixtures of any of the pharmacological or therapeutic agents described above can be used in the compositions of the present invention. Generally, a total daily dosage of the

pharmacological or therapeutic agents described above can range from about 1 to about 5000 grams per day, and preferably about 1 to about 1000 grams per day in single or 2-4 divided doses.

VII. KITS

[0065] According to another aspect of the invention, kits are provided. Kits according to the invention include vessel(s) containing compounds or compositions of the invention.

[0066] The term "vessel" means any package containing compounds or compositions presented herein. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, for example, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation. In preferred embodiments, the package can be a box or wrapping.

[0067] The kit can also contain items that are not contained within the vessel but are attached to the outside of the package, for example, pipettes.

[0068] Kits may optionally contain instructions for administering compounds or compositions of the present invention to a subject having a condition in need of treatment. Kits may also comprise instructions for uses of compounds herein approved by regulatory agencies, such as the United States Food and Drug Administration. Kits may optionally contain labeling or product inserts for the present compounds. The package(s) and/or any product insert(s) may themselves be approved by regulatory agencies. The kits can include compounds in the solid phase or in a liquid phase (such as buffers provided) in a package. The kits also can include buffers for preparing solutions for conducting the methods, and pipettes for transferring liquids from one container to another.

[0069] Optionally, the kit also may contain one or more other compounds for use in combination therapies, as described here. In certain embodiments, a suitable package is a container for intravenous administration. In other embodiments, compounds are provided in an inhaler. In still other embodiments, compounds are provided in a polymeric matrix or in the form of a liposome.

VIII. ASSAYS TO ASSESS ACTIVITY

[0070] Various well known *in vitro* or *in vivo* assays may be used to evaluate the ability of invention compounds to lower concentrations of a sterol in the plasma of a mammal. For example, to assess the ability of invention compounds to lower cholesterol levels, invention compounds may be administered to hamsters and after a period of time, such as 1 week, blood can be collected from the hamsters and plasma cholesterol levels determined using standard techniques.

[0071] The following examples are provided to further illustrate aspects of the invention. These examples are non-limiting and should not be construed as limiting any aspect of the invention.

EXAMPLES

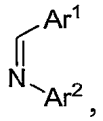
[0072] Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. THF and toluene were distilled from sodium/benzophenone ketyl. Anhydrous DMF was stored over activated 4Å molecular sieves before use. Dichloromethane was dried by distillation from phosphorus pentoxide.

[0073] Structural characterization was conducted using ^{1}H NMR spectroscopy. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on an Avance 400 spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane.

[0074] Purified compounds were analyzed for correct mass using a Finnigan LCQ mass spectrometer with ESI source. Compound identity was confirmed by the observance of the $(M+H^+)$ ion (M+1).

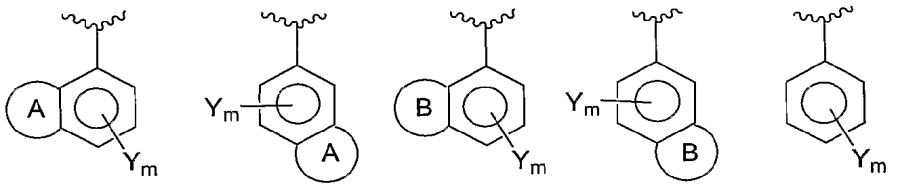
EXAMPLE 1
PREPARATION OF IMINES

[0075] Imines of the following general formula:



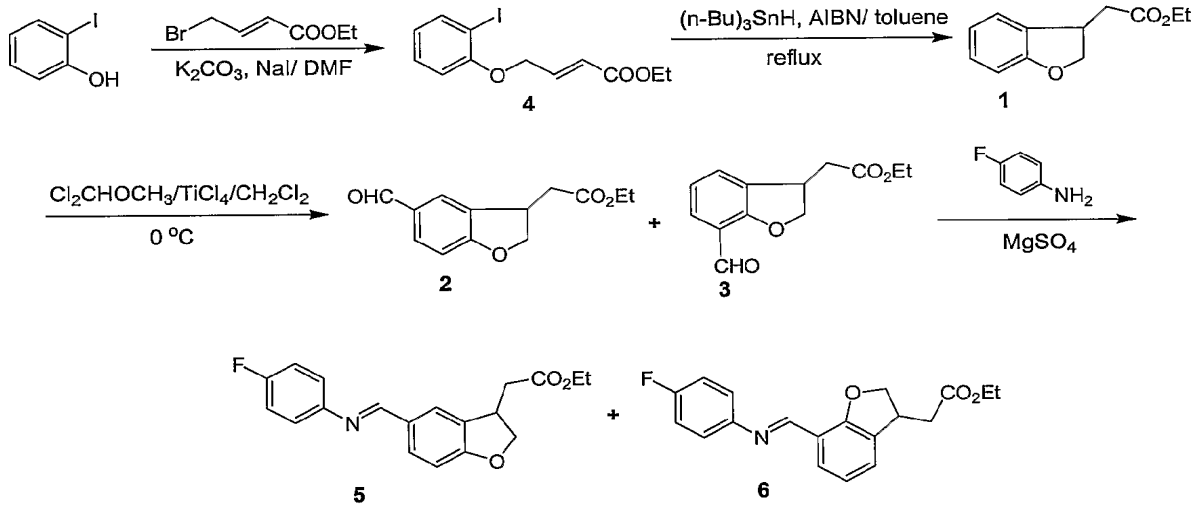
,

wherein Ar^1 and Ar^2 is selected from the following:



were prepared. Using the exemplary procedure described below and as depicted in Scheme 3, diarylimine compounds **5** and **6** were obtained.

SCHEME 3



A. 4-(2-Iodo-phenoxy)-but-2-enoic acid ethyl ester (**4**)

[0076] To a solution of 2-iodo-phenol (45 g, 0.135 mol) in DMF (200 mL), K_2CO_3 (22.5 g, 0.162 mol) and NaI (4.1 g, 0.027 mol) were added, and the reaction mixture was stirred at room temperature overnight. The mixture was then poured into water, extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate. After filtration and evaporation, the residue was purified by column chromatography on silica gel to give **4** (37 g, 82%). ^1H NMR ($CDCl_3$) δ7.70 (d, J= 7.8 Hz, 1H), 7.28 (t, J= 7.8 Hz, 1H), 7.08 (dt, J=16 Hz, J= 3.0 Hz, 1H), 6.75 (m, 2H), 6.42 (d, J= 16 Hz, 1H), 4.75 (m, 2H), 4.15 (q, J= 7.2 Hz, 2H), 1.24 (t, J= 7.2 Hz, 3H).

B. (2,3-Dihydro-benzofuran-3-yl)-acetic acid ethyl ester (**1**)

[0077] To a solution of **4** (6.64 g, 0.02 mol) and AIBN (0.328 g, 0.002 mol) in toluene (50 mL), $(n\text{-}Bu)_3SnH$ (10.92 g, 0.03 mol) was added. The mixture was heated at 80°C for 3h. The mixture was then cooled to room temperature, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography on silica gel to afford **1** (3.9 g, 95%). ^1H NMR ($CDCl_3$) δ7.15 (m, 2H), 6.88 (t, J= 6.8 Hz, 1H), 6.70 (d, J= 6.8 Hz, 1H), 4.75 (t, J= 7.2 Hz, 1H), 4.28 (t, J= 7.2 Hz, 1H), 4.15 (q, J= 7.8 Hz, 2H), 3.88 (m, 1H), 2.80 (dd, J= 7.8 Hz, J= 3.6 Hz, 1H), 2.60 (dd, J= 7.8 Hz, J= 5.6 Hz, 1H), 1.24 (t, J= 7.8 Hz, 3H).

C. (5-Formyl-2,3-dihydro-benzofuran-3-yl)-acetic acid ethyl ester and (**2**) and (7-Formyl-2,3- dihydro-benzofuran-3-yl)-acetic acid ethyl ester (**3**)

[0078] To a solution of **1** (6.18 g, 30 mmol) in dichloromethane (200 mL) at 0°C, Cl_2CHOCH_3 (5.16 g, 45 mmol) and $TiCl_4$ (17 g, 90 mmol) were added. After 1h, the mixture was poured into ice water, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by column chromatography on silica gel to afford a mixture of **2** and **3** (5:1) (5.6 g, 80%), whose ratio was measured by the integration in ^1H NMR spectrum. For compound **2**, ^1H NMR ($CDCl_3$): δ9.83 (s, 1H), 7.75 (s, 1H), 7.70 (d, J= 6.8 Hz, 1H), 6.90 (d, J= 6.8 Hz, 1H), 4.90 (m, 1H), 4.40 (m, 1H), 4.15 (q, J= 7.8 Hz, 2H), 3.90 (m, 1H), 2.83 (m, 1H), 2.60 (m, 1H), 1.24 (t, J= 7.8Hz, 3H). For compound **3**, ^1H NMR ($CDCl_3$): δ10.20 (s, 1H), 7.62 (d, J= 6.8 Hz, 1H), 7.40 (d, J= 6.8 Hz, 1H), 6.96 (t, J= 6.8 Hz, 1H), 4.90 (m, 1H), 4.48 (m, 1H), 4.15 (q, J= 7.8 Hz, 2H), 3.90 (m, 1H), 2.80 (m, 1H), 2.60 (m, 1H), 1.24 (t, J= 7.8 Hz, 3H).

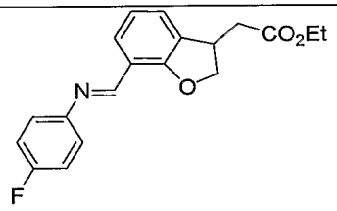
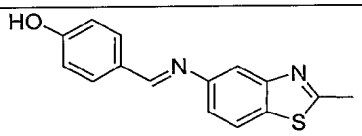
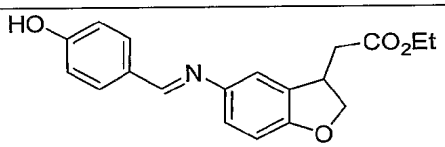
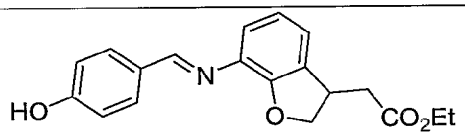
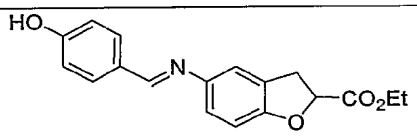
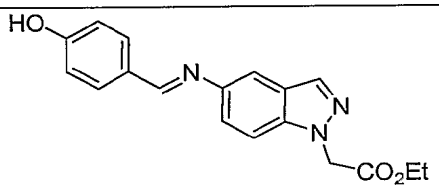
D. {5-[(4-Fluoro-phenylimino)-methyl]-2,3-dihydro-benzofuran-3-yl}-acetic acid ethyl ester (**5**) and {7-[(4-Fluoro-phenylimino)-methyl]-2,3-dihydro-benzofuran-3-yl}-acetic acid ethyl ester (**6**)

[0079] To a solution of **2** and **3** (5.8 g, 24.7 mmol) and p-fluoroaniline (2.57 mL, 27.1 mmol) in dichloromethane (100 mL), anhydrous $MgSO_4$ (30 g, 0.247 mol) was added. The mixture was heated at reflux for 12 h. The mixture was then cooled to room temperature, filtered through Celite® and the filtrate was evaporated in vacuum, and then crystallized to give **5** and **6** (5:1) (7.42 g, 90%), whose ratio was measured by the integration in ^1H NMR spectrum. For compound **5**, ^1H NMR ($CDCl_3$): δ8.42 (s, 1H), 7.82 (s, 1H), 7.60 (d, J= 6.8 Hz, 1H), 7.18 (m, 2H), 7.04 (m, 2H), 6.86 (d, J= 6.8 Hz, 1H), 4.88 (m, 1H), 4.38 (m, 1H), 4.18 (q,

J= 7.2 Hz, 2H), 3.92 (m, 1H), 2.86 (m, 1H), 2.60 (m, 1H), 1.24 (t, J= 7.2 Hz, 3H). For compound **6**, ^{1}H NMR ($CDCl_3$): δ8.62 (s, 1H), 7.84 (d, J= 6.8 Hz, 1H), 7.38 (t, J= 6.8 Hz, 1H), 7.18 (m, 2H), 7.04 (m, 2H), 6.96 (d, J= 6.8 Hz, 1H), 4.76 (m, 1H), 4.38 (m, 1H), 4.18 (q, J= 7.2 Hz, 2H), 3.86 (m, 1H), 2.86 (m, 1H), 2.60 (m, 1H), 1.24 (t, J= 7.2 Hz, 3H).

[0080] Various imines are prepared in an analogous manner as described above, including the exemplary compounds illustrated below in Table 1.

TABLE 1. Exemplary Imines

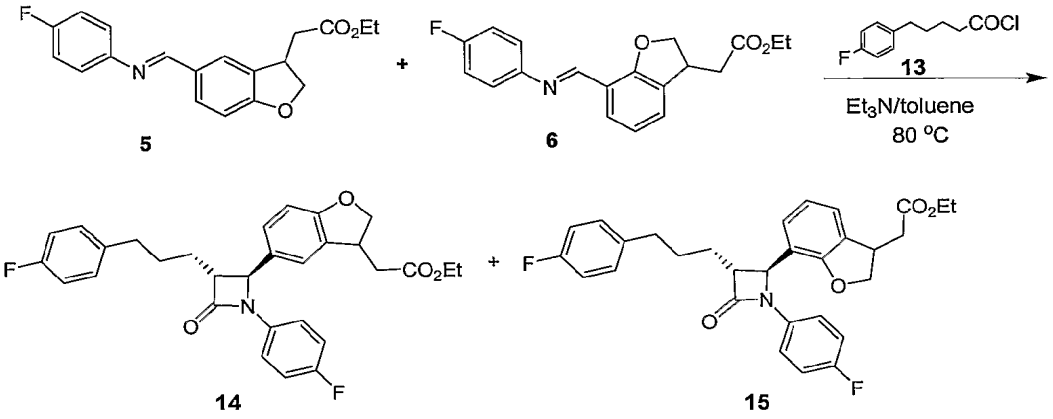
Compound Name	Compound Structure
7	
8	
9	
10	
11	
12	

EXAMPLE 2

PREPARATION OF AZETIDINONE COMPOUNDS

[0081] Imine compounds were condensed with 5-(4-Fluoro-phenyl)-pentanoyl chloride **13** to obtain azetidinone-containing compounds. As shown in the exemplary route depicted in Scheme 4 and described below, representative azetidinone-containing compounds **14** and **15** were prepared.

SCHEME 4

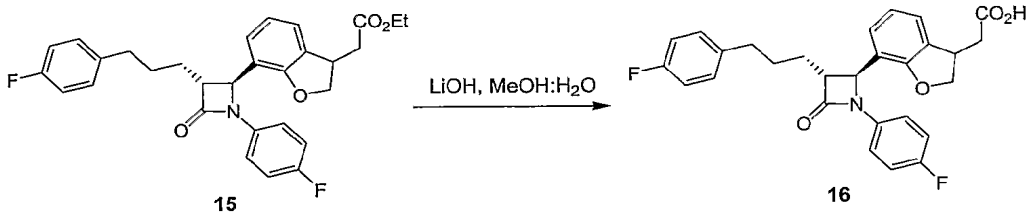


A. (5-{1-(4-Fluoro-phenyl)-3-[3-(4-fluoro-phenyl)-propyl]-4-oxo-azetidin-2-yl}-2,3-dihydro-benzofuran-3-yl)-acetic acid ethyl ester (14) and (7-{1-(4-Fluoro-phenyl)-3-[3-(4-fluoro- phenyl)-propyl]-4-oxo-azetidin-2-yl}-2,3-dihydro-benzofuran-3-yl)-acetic acid ethyl ester (15)

[0082] To a solution of **5** and **6** (7.8 g, 23.8 mmol) and Et_3N (4.82 g, 47.6 mmol) in toluene (40 mL), a solution of 5-(4-Fluoro-phenyl)-pentanoyl chloride **13** in toluene (20 mL) over 1.5h at 80°C was added dropwise. The mixture was then stirred for 12h at 80°C, and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica gel to give **14** (7.16 g, 59.6%) and **15** (0.77 g, 6.4%). For compound **14**, ^{1}H NMR ($CDCl_3$): δ7.24 (m, 2H), 7.10 (m, 4H), 6.92 (m, 4H), 6.78 (d, J= 7.8 Hz, 2H), 4.78 (t, J= 9.1 Hz, 1H), 4.6 (s, 1H), 4.34 (m, 1H), 4.18 (m, 2H), 3.84 (m, 1H), 3.06 (m, 1H), 2.60 (m, 4H), 1.80 (m, 4H), 1.24 (m, 3H). Mass spectrometry data for compound **14**: 506 (M+1). For compound **15**, ^{1}H NMR ($CDCl_3$): δ7.24 (m, 2H), 7.10 (m, 3H), 7.01 (d, J= 7.2 Hz, 1H), 6.96 (m, 4H), 6.83 (t, J= 7.2 Hz, 2H), 4.88 (m , 2H), 4.20 (m, 3H), 3.94 (m, 1H), 3.23 (m, 1H), 2.70 (m, 4H), 1.80 (m, 4H), 1.24 (m, 3H). Mass spectrometry data for compound **15**: 506 (M+1).

[0083] Compound **15** was hydrolyzed to yield compound **16** using the following exemplary route depicted in Scheme 5 and described below.

SCHEME 5

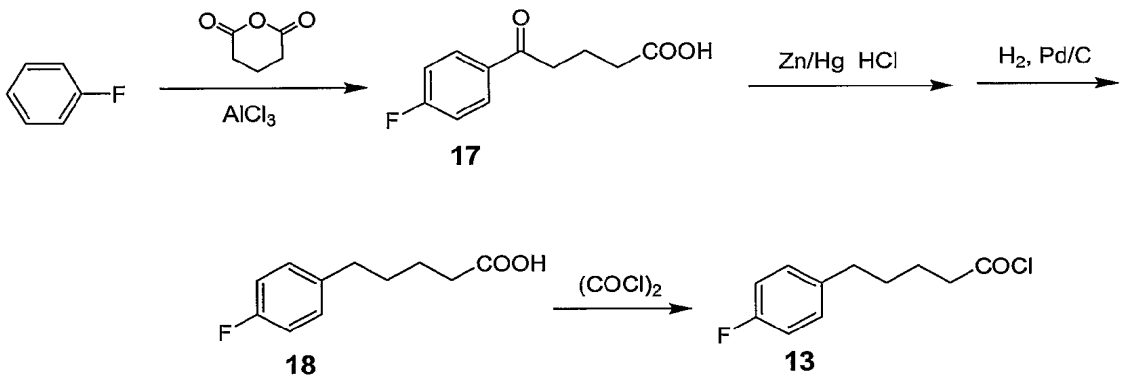


B. (7-{1-(4-Fluoro-phenyl)-3-[3-(4-fluoro-phenyl)-propyl]-4-oxo-azetidin-2-yl}-2,3-dihydro-benzofuran-3-yl)-acetic acid (**16**)

[0084] To a solution of compound **15** (0.33 g, 0.65 mmol) in THF:H_2O (2:1, 5 mL), lithium hydroxide hydrate (0.270 g, 6.5 mmol) was added at room temperature. After 1h, the mixture was poured into water, extracted with ethyl acetate, and the combined layers were washed with brine, and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by column chromatography on silica gel to give **16** (0.20 g, 65%). ^{1}H NMR ($CD_3OD + D_2O$): δ7.24 (m, 2H), 7.20 (d, J= 6.8 Hz, 2H), 7.16 (m, 2H), 7.08 (d, J = 6.8 Hz, 2H), 6.92 (m, 4H), 6.82 (t, J = 6.8 Hz, 2H), 4.88 (m, 1H), 4.70 (m, 1H), 4.34 (m, 1H), 3.84 (m, 1H), 3.30 (m, 1H), 2.60 (m, 2H), 2.50 (m, 2H), 1.80 (m, 4H). Mass spectrometry data for compound **1**: 478 (M+1).

[0085] Intermediate 5-(4-Fluoro-phenyl)-pentanoyl chloride **13** was prepared according to the following exemplary route depicted in Scheme 6 and described below.

SCHEME 6



C. 5-(4-Fluoro-phenyl)-5-oxo-pentanoic acid (**17**)

[0086] Under a nitrogen atmosphere, a mixture of aluminum chloride (275.1 g, 2.1 mol) in dichloromethane (1000 mL) was stirred and cooled to -10°C. A solution of glutaric anhydride

(105 g, 0.91 mol) was added dropwise to the cooled mixture with stirring. After 5h at -10°C, the reaction mixture was poured into 3.5M HCl (1000 mL), and the product was extracted into dichloromethane. The extract was washed with cold saturated aqueous sodium carbonate, and the aqueous layers were acidified and extracted with dichloromethane. The extract was washed with brine, dried over anhydrous sodium sulfate and evaporated in vacuo without further purification to give **17** (118g, 61.3%) as a crystal. ^{1}H NMR ($CDCl_3$): δ8.00 (dd, J= 8.2 Hz, J= 5.2 Hz, 2H), 7.12 (t, J= 8.2 Hz, 2H), 3.05 (t, J= 7.2 Hz, 2H), 2.50 (t, J= 7.2 Hz, 2H), 2.0 (m, 2H).

D. 5-(4-Fluoro-phenyl)-pentanoic acid (**18**)

[0087] Amalgamated zinc was freshly prepared by shaking for five minutes from a mixture of mossy zinc (260 g, 4 mol), mercuric chloride (46 g, 0.17 mol), water (60 mL), and concentrated hydrochloric acid (20 mL). To the amalgamated zinc in toluene (500 mL), compound **17** (112 g, 0.53 mol) and concentrated hydrochloric acid (150 mL) was added, and the resulting mixture was heated to reflux overnight. After separation, the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* without further purification. The crude product was dissolved in methanol (500 mL) and 10% palladium on carbon (5 g) was added. The mixture was stirred at 1 atm pressure overnight until compound **18** was obtained exclusively. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to afford **18** (93 g, 89%). ^{1}H NMR ($CDCl_3$): δ7.20 (dd, J= 8.4 Hz, J= 4.2 Hz, 2H), 6.96 (t, J= 8.4 Hz, 2H), 2.61 (m, 2H), 2.30 (m, 2H), 1.62 (m, 2H); 12: δ7.42 (dd, J= 8.4 Hz, J= 4.2 Hz, 2H), 6.96 (t, J= 8.4 Hz, 2H), 6.42 (t, J= 16 Hz, 1H), 6.20 (dt, J= 16 Hz, J= 6.4 Hz, 2H), 2.42 (m, 4H).

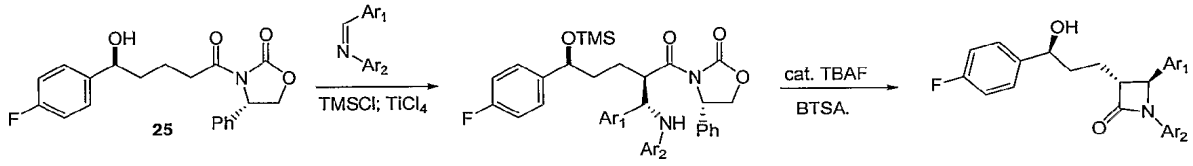
E. 5-(4-Fluoro-phenyl)-pentanoyl chloride (**13**)

[0088] To a solution of **18** (7.0 g, 36 mmol) in CH_2Cl_2 (100 mL), oxalyl chloride (5.6 g, 44 mmol) and a drop of DMF was slowly added, and the solution was heated to mild reflux. After 2h, the reaction mixture was concentrated *in vacuo* to afford the acid chloride **13** as an oil.

EXAMPLE 3
PREPARATION OF AZETIDINONE COMPOUNDS

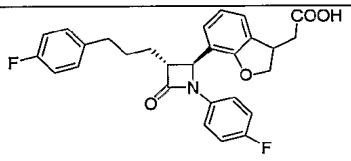
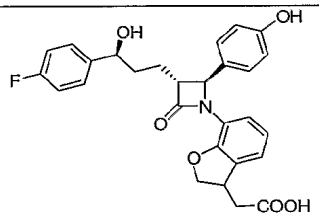
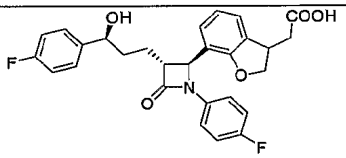
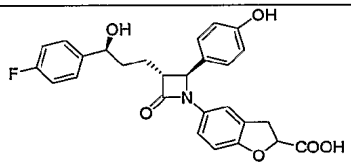
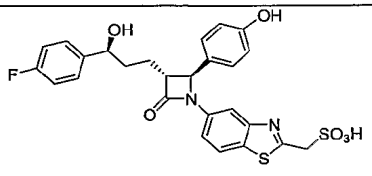
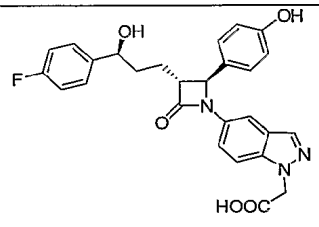
[0089] Azetidinone-containing compounds may also be prepared according to the exemplary procedure depicted in Scheme 7 below. Imine compounds prepared according to the exemplary procedure described in Example 1 are combined with chiral compound **25** to obtain azetidinone-containing compounds.

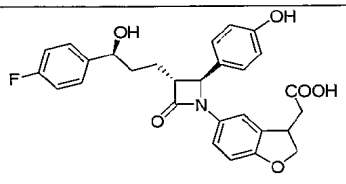
SCHEME 7



[0090] Azetidinone-containing compounds obtained by the route of Scheme 7 can be further hydrolyzed to introduce various moieties, such as carboxylic acid groups, or chemically manipulated to introduce other moieties, such as sulfonic acid groups. Illustrated below in Table 2 are exemplary azetidinone-containing compounds which are obtained using the representative preparative route illustrated in Scheme 7.

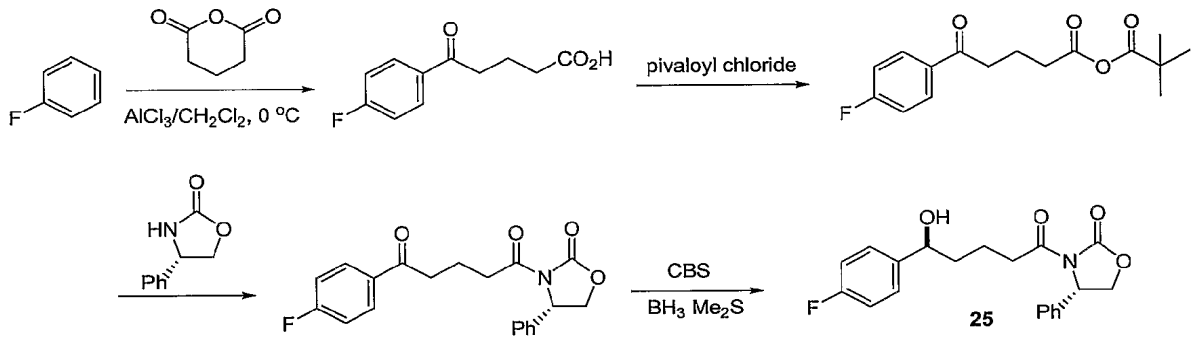
TABLE 2. Exemplary Azetidinones

Compound Name	Compound Structure	Compound Name	Compound Structure
16		**22**	
19		**23**	
20		**24**	

Compound Name	Compound Structure	Compound Name	Compound Structure
21			

[0091] Intermediate chiral compound **25** is prepared according to the exemplary route depicted below in Scheme 8.

SCHEME 8



EXAMPLE 4

EVALUATION OF CHOLESTEROL LOWERING ACTIVITY

[0092] The following exemplary assay is used to determine the ability of invention compounds to lower concentration of a sterol in the plasma of a mammal.

[0093] Male golden syrian hamsters (Charles River Labs, Wilmington, MA, U.S.A.) weighing between 100 – 125 g are fed rodent chow until study onset. At study onset, animals are separated into groups ($n = 4 – 6$ per group) based on body weight, and fed chow supplemented with 0.5% cholesterol (Purina) for 7 days. Invention compounds (1-10 mg/kg) are orally administered qd or bid in 0.2 ml carboxymethylcellulose. After 7 days, animals are sacrificed by intracardiac exsanguination after anesthesia, blood is collected, and plasma is separated by low speed centrifugation at 4°C and frozen at -80°C. Total cholesterol and LDL cholesterol levels are analyzed using standard procedures on a clinical chemistry autoanalyzer (Olympus AU640 + manufacturer supplied reagents).

[0094] The invention illustratively described herein may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of

limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0095] The contents of the articles, patents, and patent applications, and all other documents and electronically available information mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference. Applicants reserve the right to physically incorporate into this application any and all materials and information from any such articles, patents, patent applications, or other documents.

[0096] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including," containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

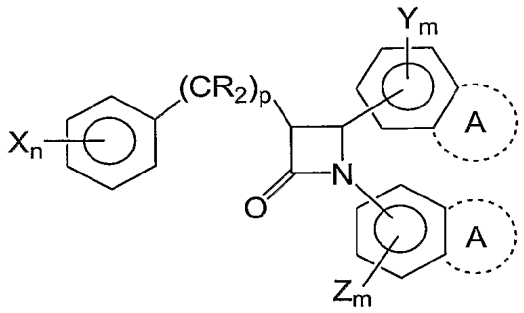
[0097] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0098] In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0099] Other embodiments are set forth within the following claims.

WHAT IS CLAIMED IS:

1. A compound corresponding to Formula (**I**):



(**I**)

and stereoisomers, tautomers, solvates, prodrugs, pharmaceutically acceptable salts and mixtures thereof; wherein:

A at each occurrence independently forms an optionally substituted fused heterocycle with the phenyl to which it is attached, wherein the dashed lines represent an optionally present A, provided, however, that at least one A is present;

R at each occurrence is selected from the group consisting of H, halogen, OH, NH_2, NO_2, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

X, Y, and Z at each occurrence are independently selected from the group consisting of halogen, OH, alkyl, alkoxy, SH, thioalkyl, NH_2, and NO_2;

m at each occurrence is independently 0 to 3;

n is 0 to 5; and

p is 1 to 6.

2. The compound of claim 1, wherein at least one X is halogen.

3. The compound of claim 2, wherein X is F and n is 1.

4. The compound of claim 1, wherein at least one R is OH.

5. The compound of claim 4, wherein $(CR_2)_p$ is $-CH_2$-CH_2-CH(OH)-.

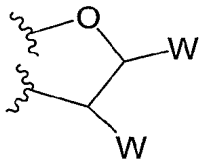
6. The compound of claim 1, wherein at least one Y is OH.

7. The compound of claim 1, wherein at least one Z is F.

8. The compound of claim 1, wherein A forms a nonaromatic, optionally substituted fused heterocycle.

9. The compound of claim 8, wherein A forms an optionally substituted fused five-membered heterocycle.

10. The compound of claim 9, wherein A is:



wherein:

W at each occurrence is independently selected from the group consisting of H, halogen, OH, alkyl, alkoxy, SH, thioalkyl, NH_2, NO_2, CN, SO_2R^1, SO_3R^2, and -J-C(O)R^3;

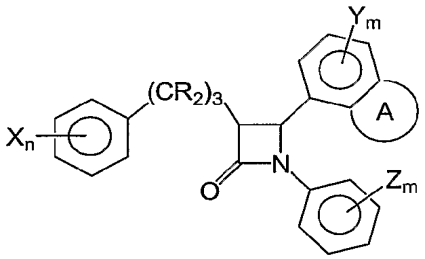
R^1 is selected from the group consisting of H, halogen, alkyl, alkoxy, aryl, heteroaryl, NH_2, NH(alkyl), and N(alkyl)$_2$;

R^2 is selected from the group consisting of H, NH_2, NH(alkyl), and N(alkyl)$_2$;

J is selected from the group consisting of a covalent bond and C_1-C_3 alkylene; and

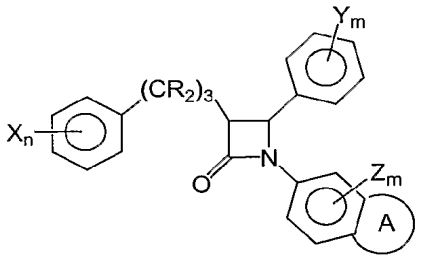
R^3 is selected from the group consisting of OH, alkoxy, NH_2, NH(alkyl), and N(alkyl)$_2$.

11. The compound of claim 1, corresponding to Formula (**II**):



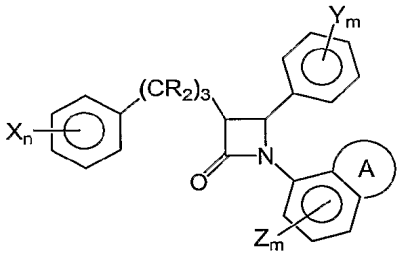
(II).

12. The compound of claim 1, corresponding to Formula (**III**):



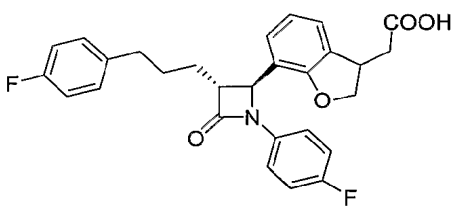
(**III**).

13. The compound of claim 1, corresponding to Formula (**IV**):



(**IV**).

14. The compound of claim 1 selected from the group consisting of: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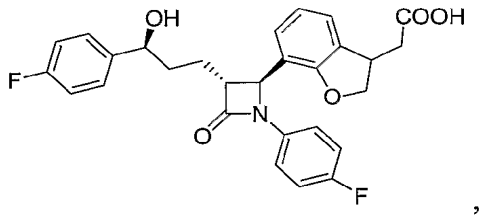
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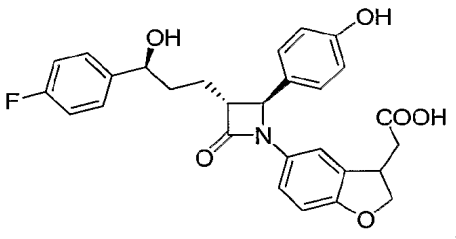
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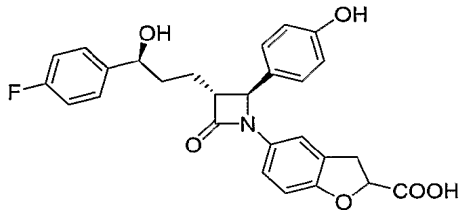
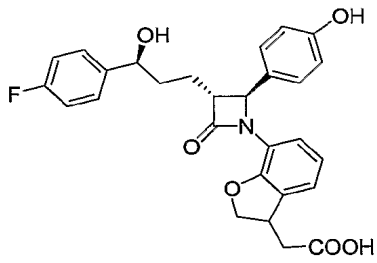

, and

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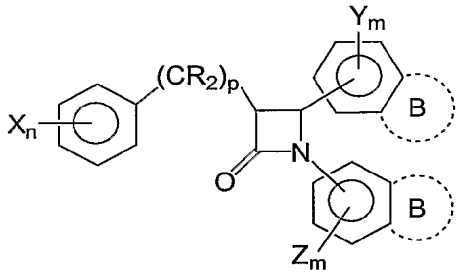
15. A compound of claim 1 corresponding to Formula (V):



(V)

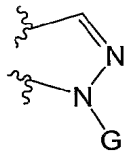
wherein:

B at each occurrence is independently a G-substituted five-membered fused heterocycle, wherein the dashed lines represent an optionally present B, provided, however, that at least one B is present;

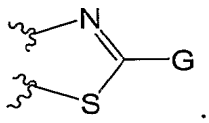
G is selected from the group consisting of -(C_1-C_3 alkylene)-C(O)R^4 and -(C_1-C_3 alkylene)-SO_2R^4; and

R^4 is selected from the group consisting of H, hydroxyl, halogen, alkyl, alkoxy, aryl, heteroaryl, NH_2, NH(alkyl), and $N(alkyl)_2$.

16. The compound of claim 15, wherein B is selected from the group consisting of:



and



.

17. The compound of claim 16, wherein G is selected from the group consisting of $-CH_2-C(O)R^4$ and $-CH_2-SO_2R^4$.

18. The compound of claim 15, wherein at least one X is halogen.

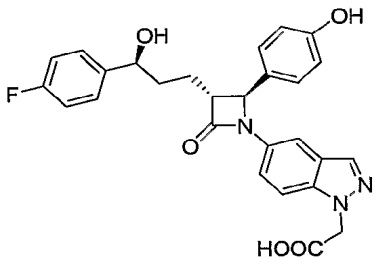
19. The compound of claim 18, wherein X is F and n is 1.

20. The compound of claim 15, wherein each at least one R is OH.

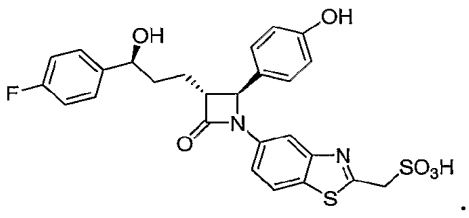
21. The compound of claim 20, wherein $(CR_2)_p$ is $-CH_2-CH_2-CH(OH)-$.

22. The compound of claim 15, wherein Y is OH and m is 1.

23. The compound of claim 15 selected from the group consisting of:



and



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24. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

25. A composition comprising the compound of claim 15 and a pharmaceutically acceptable carrier.

26. A method of treating diabetes comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

27. A method of treating obesity comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

28. A method of lowering concentration of a sterol in plasma of a mammal in need of such treatment, the method comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.

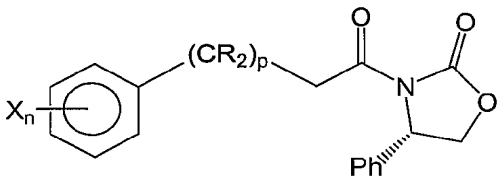
29. A method of lowering cholesterol levels in a mammal in need of such treatment, the method comprising administering to said mammal a therapeutically effective amount of the compound of claim 1.

30. A method of treating atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of the compound of claim 1.

31. A method for preparing the compound of claim 1, said method comprising:

contacting a compound of Formula (**VI**) with an imine of Formula (**VII**) or (**VIII**), in the presence of a Lewis acid, a silylating agent, and a fluoride ion catalyst,

wherein said compound of Formula (**VI**) corresponds to the following structure:



(VI)

wherein:

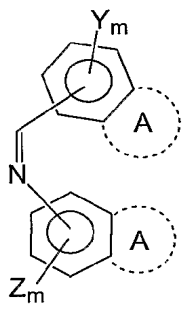
R at each occurrence is independently selected from the group consisting of H, halogen, OH, NH_2, NO_2, C_1-C_3 alkyl, and C_1-C_3 alkoxy;

X is optionally present, and when present at each occurrence is independently selected from the group consisting of halogen, OH, alkyl, alkoxy, SH, thioalkyl, NH_2, and NO_2;

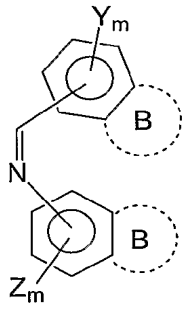
n is 0 to 5; and

p is 1 to 6;

wherein said imine of Formula **(VII)** or **(VIII)** corresponds to the following structures:



(VII)



(VIII)

wherein:

A at each occurrence independently forms an optionally substituted fused heterocycle with the phenyl to which it is attached, wherein the dashed lines represent an optionally present A, provided, however, that at least one A is present;

B at each occurrence is independently a G-substituted five-membered fused heterocycle, wherein the dashed lines represent an optionally present B, provided, however, that at least one B is present;

G is selected from the group consisting of $-(C_1\text{-}C_3$ alkylene)-$C(O)R^4$ and-$(C_1\text{-}C_3$ alkylene)-SO_2R^4;

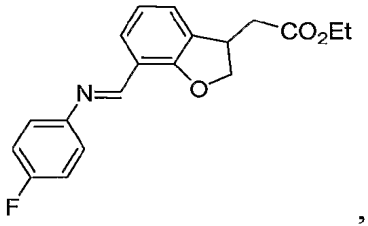
R^4 is selected from the group consisting of H, hydroxyl, halogen, alkyl, alkoxy, aryl, heteroaryl, NH_2, NH(alkyl), and $N(alkyl)_2$,

Y and Z are optionally present, and when present at each occurrence are independently selected from the group consisting of halogen, OH, alkyl, alkoxy, SH, thioalkyl, NH_2, and NO_2; and

m at each occurrence is independently 0 to 3.

32. The method of claim 31, wherein said Lewis acid is titanium (IV) chloride, said silylating agent is trimethylsilyl chloride (TMSCl), and said fluoride ion catalyst is tetrabutyl ammonium fluoride (TBAF).

33. The method of claim 31, wherein the imine of Formula (**VII**) or (**VIII**) is selected from the group consisting of:



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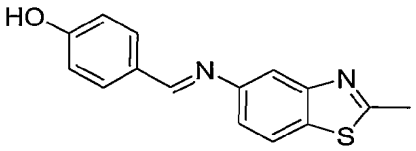

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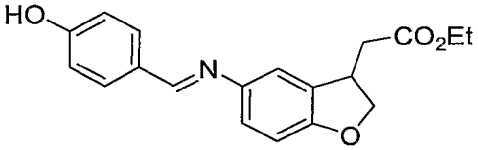

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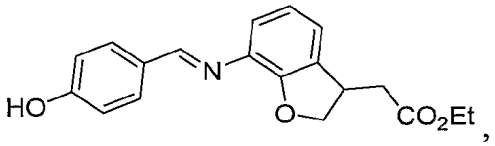

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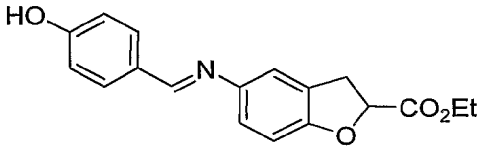

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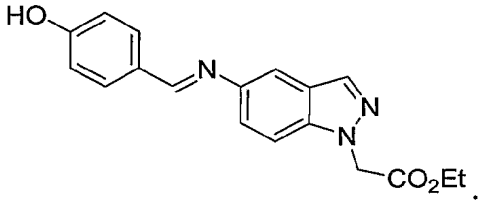

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